REMARKS

Applicants acknowledge that the restriction requirement is now made final. Accordingly, claims 1-33 and 35-38 are withdrawn without prejudice. The Examiner has examined pending claims 34, 39, and 40. Applicants reserve the right to pursue the subject matter of the withdrawn claims in the present or future applications.

Applicants file herewith a petition under 37 CFR 1.84(a)(2) to include color drawings for Figures 1-9 and 11. Accordingly, Applicants enclose three copies of the color drawings along with payment of the fee set forth in 37 CFR 1.17(h).

Claim rejections under 35 USC § 112, first paragraph

The Examiner has rejected claims 34, 39, and 40 under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the enablement requirement. Specifically, the Examiner states that the "specification fails to provide any details or reduce to practice concerning how to use a bone marrow mobilization therapy for ameliorating any one symptom of any one neuronal deficiency, and thus fails to provide an enabling disclosure for what is now claimed." The Examiner then cites several publications to argue that, although around the time of filing bone marrow cells were shown to have the potential to differentiate into neuronal cells, which have the potential for neuron regeneration, the state of the art was not and has not developed to the extent that the specification enables "a therapeutic use for ameliorating any symptom of a neuronal disorder at the time of the instant priority date" (page 6 of the Office Action).

Applicants disagree. The Examiner cites Sigurjonsson et al. to support the argument that "bone marrow mobilization treatment or bone marrow transplantation was far from treating any neuronal diseases". In column 2, page 5227, first paragraph of Sigurjonsson et al.—the section the Examiner cited—Sigurjonsson et al. describe certain limitations of the experimental systems used to study neuronal differentiation and neuronal phenotype of HSCs injected into rodents or studied in vitro. The statements—"The characterization of neuronal phenotype in all these studies has been limited to the expression of selected molecular markers. Functional phenotypic features and integration into synaptic networks have not been demonstrated"—indicate that neuronal features and functional phenotypes of HSC-derived neurons have not been tested, not

that they do not exist. In addition, based on their studies in the chicken embryo system, Sigurjonsson et al. conclude that "the microenvironment in the regenerating spinal cord of the chicken embryo stimulates *substantial proportions* of adult human HSCs to differentiate into *full-fledged* neurons" (abstract, *emphasis added*). The Examiner additionally argues that the rate of neuronal differentiation reported in the art is low (although Sigurjonsson et al. achieved a relatively high a rate). While the rate of HSC integration in the brain in the studies cited by Sigurjonsson et al. and the rate of contribution of bone marrow-derived cells to brain neurons in the present application may be arguably "low" (due to its absolute value), this does not necessarily equate with a low rate of success in the clinic or a low probability of ameliorating at least one symptom of a neuronal deficiency or disorder. The integration rate of bone marrow-derived cells into the central nervous system demonstrated by other artisans and in the present application suggests that perhaps in the clinic, multiple treatments or "doses" of a cell-mobilization therapy may be required to ameliorate or improve a symptom of a neuronal deficiency or disorder. In that regard, the exact dose or number of treatments of a cell-mobilization therapy required to achieve the recited method outcome—i.e., the treatment of a neuronal deficiency wherein at least one symptom of the neuronal deficiency is improved—may vary from subject to subject and may depend on the particular neuronal deficiency being treated. The Patent Office does not require that such details of a therapeutic method be known in order for the method to be patentable (see below MPEP 2107), and Applicant acknowledges these clinical challenges in the publication cited by the Examiner (*Nat. Cell Bio.* 2004 (6): 810-816).

Accordingly, the specification teaches, and fully enables, a method of treating a neuronal deficiency comprising administering to a subject a bone marrow cell mobilization therapy which induces formation of bone marrow-derived neurons in the nervous system of the subject and subsequently results in the amelioration or improvement of at least one symptom of the neuronal deficiency. For example, on page 37, starting at line 22, the specification teaches that bone mobilization treatments, including treatments comprising G-CSF, are well-known in the art and cites various sources, among them Chao et al. Though the Examiner objects to the reference to Chao et al., stating that "Chao et al. use G-CSF in a completely different circumstance where the patient underwent chemotherapy and administering growth factor G-CSF promoted regeneration of new blood cells" and thus the "Chao reference does not provide any teaching regarding treating a neuronal disease/symptom" (page 5 of the Office Action), the reference to Chao et al.

serves to provide support for an exemplary bone mobilization treatment, not for the outcome of such treatment (indeed, the novel outcome of bone mobilization therapy, and of other treatments with bone marrow-derived cells, is a subject of the present application). Further, G-CSF treatment has been demonstrated to produce a "significant mobilization of stem cells" in humans (abstract, Zohlnhofer et al. JAMA. 2006 Mar 1;295(9):1003-10 (article attached as Exhibit 1)), and in mice, G-CSF increased peripheral blood pluripotent hematopoietic stem cells by 250-fold (abstract, Bodine et al. 1994 Blood (84): 1482-1491, Exhibit 2). As further evidence that bone mobilization treatment can be a substitute for injection or treatment with bone marrow cells, Orlic et al. demonstrated that bone mobilization treatment achieved similar clinical effects as injected bone marrow cells in promoting myocardial repair (2001 PNAS (98): 10344-10349, abstract attached as Exhibit 3).

In addition, the specification demonstrates that bone marrow-derived cells contribute to neuronal cells. See, for example, Example 1, where treatment with GFP+ bone marrow-derived cells resulted in cells in the brain that lacked hematopoietic cell markers (page 40, line 19), and Example 2, where GFP+ bone marrow-derived cells expressed neuronal markers and morphology, including extensions (page 41 line 21 to page 42 Table 1), and Example 3, where in humans, bone marrow-derived cells contributed to Purkinje cells (page 46, line 16). Each of these findings alone, along with the knowledge in the art that bone mobilization treatments result in the migration of cells from the bone marrow into the circulation (e.g., bone mobilization treatments are in fact used to collect cells for autologous and allogeneic donations in hematopoietic stem cell transplantation), fully enable the claimed invention.

The Examiner states that the specification "fails to teach the efficacy of such BM mobilization processes, whether it is sufficient to the extent that any *clinical benefit* could be observed" (page 7, first paragraph of Office Action, *emphasis added*). It appears the Examiner's rejection relates to the intended therapeutic use and an alleged lack of enablement for the claimed therapeutic use. Regarding the utility of claimed therapeutic uses, MPEP 2107 states

> ... therapeutic utility sufficient under the patent laws is not to be confused with the requirements of the FDA with regard to safety and efficacy of drugs to marketed in the United States...Usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans.

Were we to require Phase II testing in order to prove utility, the associated costs would prevent many companies from obtaining patent protection on promising new inventions, thereby eliminating an incentive to pursue, through research and development, potential cures in many crucial areas such as the treatment of cancer.

Accordingly, the claimed methods taught in the specification and based on the evidence and support provided in the examples are fully enabled as a person skilled in the art can practice the claimed methods without undue experimentation. Likewise, the claimed therapeutic uses are enabled, as performing the claimed methods achieves the predicted therapeutic outcome. Accordingly, the disclosure satisfies both the enablement and utility requirements and Applicants request the Examiner withdraw this rejection.

Claim rejections under 35 USC § 112, second paragraph

The Examiner has rejected claims 34, 39, and 40 under 35 U.S.C. § 112, second paragraph, contending that these claims are indefinite for failing to clearly set forth the method steps. In particular, the Examiner argues that "it is unclear what step the 'mobilization therapy' includes, and thus the metes and bounds of the claims are unclear". Applicants disagree. Many different bone mobilization therapies are practiced in the clinic and are encompassed by the claimed methods (see, for example, Cashen et al. Curr Hematol Rep. 2004 Nov;3(6):406-12 (abstract attached as Exhibit 4) and Nervi et al. 2006 J Cell Biochem e-publication (article attached as Exhibit 5)). For example, the specification teaches that "bone marrow cell mobilization protocols are well known in the art" (page 37, lines 23-34) and continues by providing exemplary protocols comprising G-CSF (pages 37-38 of the specification). Because bone mobilization may be performed in a variety of ways using a variety of agents that are known in the art, and while the claimed method is not limited to any particular mobilization treatment, Applicants believe reciting specific method steps for administering bone mobilization treatment is inappropriate. Moreover, because the skilled artisan would know, based on the skill in the relevant art, what steps constitute "administering a bone marrow cell mobilization therapy", the metes and bounds of the claims are clear. Applicants therefore request withdrawal of this rejection.

CONCLUSION

In view of at least the forgoing remarks, Applicants request reconsideration of the pending claims. Please charge any fees due to our Deposit Account No. 18-1945, under Order No. SUPP-P01-011, from which the undersigned is authorized to draw.

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Respectfully submitted,

By _____

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